REMARKS

Applicants would like to thank Examiner Kim for the phone conference held to discuss the remaining rejections in the previous Office Action. During the phone conference on May 19, 2006, Examiner Kim informed Applicants' representative that the prior art rejections would most likely be withdrawn if arguments for overcoming the rejections were provided in writing.

Applicants would like to thank the Examiner for vacating the finality of the previous Office Action dated January 24, 2006.

Status of the Claims

Claims 106-159, and 161 are currently pending in the present application. Claims 1-105 and 160 have been canceled without prejudice or disclaimer of the subject matter claimed therein.

Amendments to the Specification

The specification has been amended to update the status of the related applications and to correct inadvertent typographical errors. The amendment to the specification does not introduce prohibited new matter.

Rejections of the Claims Under 35 U.S.C. § 112, First Paragraph

Claims 142-159 and 161 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement.

The Office Action alleges that the specification does not enable a method of inducing an immune response comprising applying a formulation to more than one application area including any area of the skin comprising a first parenteral administration followed by a transdermal application and cites the factors of *In re Wands* in support of its position.

Claim 142 as it stands is directed to a method for inducing an antigen-specific immune response in a subject comprising delivering parenterally a first formulation containing an antigen to the skin of a subject; pretreating the area of the skin of the subject; and applying a second

formulation comprising an adjuvant to the area of the skin. Claims 143-159, and 161 are dependent upon claim 142 and therefore include the features of claims 142.

As discussed in the response submitted March 24, 2006, the specification describes in detail multiple applications of formulations comprising antigen and/or adjuvant to an area of skin (pages 8, lines 6-19; page 31, lines 12-15; and Examples 12, 13, 18, and 20). Specifically, the specification discloses parenteral delivery of a formulation followed by transcutaneous immunization to boost or prime an immune response induced by parenteral delivery (page 8, lines 11-15 and page 31, lines 12-15). As an example, Example 12 teaches intramuscular injection of DT to the hind thigh of mice followed by transcutaneous immunization of DT toxoid and CT, as the adjuvant, to the back of mice. Table 12 summarizes the results of Example 12 and shows that transcutaneous immunization is useful in boosting or priming an immune response induced by other routes of delivery. Specifically, Table 12 shows that mice (#8568 to #8572) who received intramuscular injection of the antigen followed by transcutaneous immunization of the antigen and adjuvant induced an immune response that is 60 times higher than that of mice (#8563 to #8567) who received only an intramuscular injection of the antigen. Also, mice (#8568 to #8572) induced an immune response that is about 1.8 times higher than that of mice (#8558 to #8562) who received three intramuscular injections of antigen.

The Office Action alleges that Example 13 does not teach parenteral delivery. However, Example 13 discloses multiple applications of formulations at different sites and at the same site of an animal to induce an antigen-specific immune response. Specifically, in Example 13, mice were transcutaneously immunized at the right ear and the left ear or only at the left ear. As shown in Table 13 (page 64), Group A mice transcutaneously immunized with antigen (BSA) at one ear and adjuvant (CT) at the other ear developed an immune response to the antigen that is 30 times higher than Group G mice immunized with antigen only in the left ear. Likewise, Group C mice transcutaneously immunized with antigen and adjuvant in the left ear developed an immune response to the antigen that is 400 times higher than Group G mice. Although the immune response of Group A mice is lower than that of Group C mice, the immune response of Group A is significant. Moreover, the claims only require that there be an antigen-specific

immune response. The results of Example 13 show that transcutaneous immunization of antigen and adjuvant at different sites and at the same sites of an animal induces an antigen-specific immune response.

Further, Example 12 (page 60) describes parenteral delivery of a first formulation followed by transcutaneous immunization of a second formulation at a different site, as discussed above and in the response submitted on March 24, 2006.

Additionally, as discussed in the previous response dated March 24, 2006, Frech *et al.* confirm that an adjuvant, such as LT, administered as an immunostimulant patch on the skin subsequent to an influenza vaccination, improved influenza immune responses in the elderly (see Frech *et al.* Vaccine 23 (2005) 946-950). Frech *et al.* report that elderly adults who received intramuscular injection of an influenza vaccine containing HA followed by an LT patch placed 5 cm distal to the vaccine injection site showed enhanced immune response as compared to those elderly who only received vaccine injection alone (see Frech *et al.*: abstract, page 947, left column (last paragraph), Table 2). The report of Frech *et al.* supports the claimed invention of parenteral delivery of an antigen followed by application of a formulation comprising at least one adjuvant to the skin to enhance the immune response induced by the antigen.

With respect to the Wands factors cited in the Office Action, Applicants respectfully assert that given the teachings and data disclosed in the specification, the claimed invention is not unpredictable. A person of ordinary skill in the art would be able to make and use the claimed invention without undue experimentation by following the teachings of the specification. The experimentation necessary to practice the claimed invention is only routine. Therefore, the specification provides sufficient guidance in the description of the invention and disclosed examples to enable a person of ordinary skill in the art to make and use the claimed method for inducing an immune response, in the absence of evidence to the contrary.

As pointed out in the previous response, the initial burden is on the Patent Office to provide a reasonable explanation as to why the scope of protection provided by the claims is not adequately enabled by the disclosure. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). Moreover, the court in *In re Marzocchi* stated that it is incumbent upon

the Patent Office to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up its assertions with acceptable evidence or reasoning which is inconsistent with the contested statement. *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). The Office Action has not provided a reasonable explanation as to why the claims are not enabled by the specification.

Rejection of the Claims Under 35 U.S.C. § 102(b)

Claims 106, 107, 109, 110, 114-121, 124, 125, 127, 128, and 132-129 are rejected under 35 U.S.C. § 102(b) as being anticipated by WO 95/17211, as evidenced by the Skills Checklist for immunization.

Claims 106 and 124 are directed to a method of inducing an antigen-specific immune response comprising pretreating an area of the skin of a subject and applying a formulation to the treated area of the skin of a subject. Claims 107, 109, 110, 114-121, 125, 127, 128, and 132-129 are dependent upon claims 106 and 124.

The deficiencies of WO 95/17211 are discussed in the previous response dated March 24, 2006. In summary, the cited reference does not teach a method of inducing an antigen-specific immune response by applying a formulation to an area of the skin of a subject. The cited reference only teaches applying a formulation to mucosal surfaces of an organism, for example, oral or intranasal delivery of formulations comprising antigen and adjuvant, as discussed on page 1 lines 29-31 of the cited reference. In contrast, the presently claimed method involves transcutaneous immunization which comprises delivery of antigens and adjuvants through the skin. Moreover, delivery of antigens and adjuvants through the skin is different from delivery through mucosal surfaces because mucosal surfaces and the skin are structurally and functionally distinct tissues. Further, the cited reference requires the use of non-toxic mucosal adjuvants with the antigen for delivery to the mucosal surface. In contrast, a toxic adjuvant, such as CT, that cannot be used for mucosal delivery can be applied to the skin for transcutaneous immunization, the method of the present invention.

The Office Action alleges that page 12, lines 12 and 13 of the cited reference teach

applying the immunogenic composition transdermally. However, the cited reference does not enable transdermal delivery of antigenic compositions. The court has held that for a reference to anticipate, the reference must enable the claimed invention. In *Minnesota Manufacturing and Mining v. Chemque, Inc.*, the Federal Circuit held that to anticipate a claim, a reference must also enable one of skill in the art to make and use the claimed invention. See *Minnesota Manufacturing and Mining v. Chemque, Inc.*, 303 F.3d 1294 (Fed. Cir. 2002). In *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, the Federal Circuit stated that a claimed invention cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled. *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 65 USPQ2d 1385, 1416 (Fed. Cir. 2003). As discussed above, the cited reference only teaches mucosal delivery of antigens and adjuvants. The cited reference only generally states that additional formulations may be delivered by other modes of administration including transdermal application. The cited reference does not describe in detail transdermal delivery of antigenic compositions to induce an antigen-specific immune response.

The Office Action relies on the Skills Checklist for disclosing pretreatment of the skin by chemical means or by hydration means. However, the Skills Checklist does not teach transdermal delivery of antigenic compositions to induce an antigen-specific immune response.

In summary, the cited reference does not disclose the limitations required in the claims. The cited reference neither teaches delivery of an antigen through the skin nor discloses treating the skin prior to or at the same time as application of the antigen to induce an antigen-specific immune response.

Rejection of the Claims Under 35 U.S.C. § 103

A. Claims 106-108, 113, 122-126, 131, 140 and 141 are rejected under 35 U.S.C. § 103 as being unpatentable over WO 95/17211 as evidenced by Skill Checklist for immunization in view of U.S. Patent 4,810,499 ('499).

Claims 106 and 124 are directed to a method of inducing an antigen-specific immune response comprising treating an area of the skin of a subject and applying a formulation to the

treated area of the skin of a subject. Claims 107, 108, 113, 122, 123, 125, 126, 131, 140, and 141 are dependent upon claims 106 and 124.

The deficiencies of WO 95/17211 are discussed immediately above under the previous rejection. Delivery of antigens through the mucosal surface does not render obvious the delivery of antigen through the skin of a subject because the mucosal surface is structurally and functionally distinct from the skin, as discussed in detail immediately above. Moreover, the delivery of antigens/adjuvants through the mucosal surface is different from delivery through the skin because the present inventors have unexpectedly found that toxic mucosal antigens/adjuvants are non-toxic when applied to the skin, as discussed above and on page 2, lines 11-22 of the specification.

The Office Action relies on the Skills Checklist for disclosing pretreatment of the skin by chemical means or by hydration means. However, the Skills Checklist does not teach transdermal delivery of antigenic compositions to induce an antigen-specific immune response.

Further, as discussed in the previous response dated March 24, 2006, it has been reported that intranasal influenza vaccine containing LT approved for distribution and use in Switzerland has been shown to cause Bell's palsy and has been withdrawn from clinical use (R. Couch, 2004, N. Engl. J. Med., 350(9): 860; Mutsch *et al.*, 2004, N. Engl. J. Med. 350(9):896). These reports teach away from the claimed invention of using antigens/adjuvants, such as HA/LT (Example 18) and CT/Hib-PS (Example 19), for transcutaneous immunization. Accordingly, the delivery of antigens/adjuvants to the mucosal surface, such as the nasal cavity, as disclosed by WO 95/17211, does not render the claimed invention obvious.

U.S. Patent '499 is relied upon for disclosing transdermal delivery. However, U.S. Patent '499 does not cure the deficiencies of WO 95/17211. U.S. Patent '499 does not teach transdermal delivery of formulations comprising antigen and adjuvant that induce an antigen-specific immune response. U.S. Patent '499 only discloses transdermal delivery of chemicals which are small molecules. Transdermal delivery of small molecules is well known and routinely practiced, but is not analogous to transdermal delivery of antigen and adjuvant of the present invention. Chemicals are small molecules of less than 500 daltons, while antigens are

large molecules. As an example, CT is a protein antigen of about 85,000 daltons.

Accordingly, there is no motivation to combine the teachings of W0 95/17211 and U.S. Patent '499 and to modify the method disclosed in the cited references to obtain the claimed method with any reasonable expectation of success. Thus, the cited references do not render the claimed invention obvious.

B. Claims 106-108, 113, 122-126, 131, 140 and 141 are rejected under 35 U.S.C. § 103 as being unpatentable over WO 95/17211 as evidenced by Skills Checklist for immunization, in view of U.S. Patent No. 5,814,599 ('599).

Claims 106 and 124 are directed to a method of inducing an antigen-specific immune response comprising treating an area of the skin of a subject and applying a formulation to the treated area of the skin of a subject. Claims 107, 108, 113, 122, 123, 125, 126, 131, 140, and 141 are dependent upon claims 106 and 124.

The deficiencies of WO 95/17211 and the Skills Checklist are discussed above. U.S. Patent '599 does not cure the deficiencies of WO 95/17211 because U.S. Patent '599 does not disclose transdermal delivery of an antigen to induce an antigen-specific immune response. U.S. Patent '599 only discloses a method of transdermal transport of drugs.

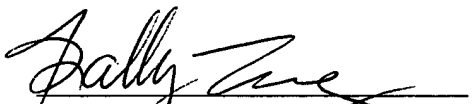
Additionally, there is no motivation to combine the teachings of the cited references because WO 95/17211 teaches applying a formulation to mucosal surfaces of an organism while U.S. Patent '599 teaches transdermal transport of drugs. As discussed above, the mucosal surface and the skin are structurally and functionally distinct tissues and that antigens/adjuvants that are toxic when delivered through the mucosal surface are non-toxic when applied to the skin. Thus, there is no motivation to combine the cited references and to obtain the claimed invention with any reasonable expectation of success. Accordingly, the cited references do not render the claimed invention obvious.

Conclusion

The foregoing amendments and remarks are being made to place the application in condition for allowance. Applicants respectfully request entry of the amendments, reconsideration, and the timely allowance of the pending claims. A favorable action is awaited. Should the Examiner find that an interview would be helpful to further prosecution of this application, they are invited to telephone the undersigned at their convenience.

If there are any additional fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 50-0310. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,
MORGAN, LEWIS & BOCKIUS LLP



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